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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
O'HARA, EILEEN B	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 10/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/978,188	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Eileen B. O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2006 and 06 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-66 and 68-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58-66 and 68-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/10/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 10, 2006 has been entered. Applicant's Supplemental Amendment filed Sept. 6, 2006 has also been entered.

Claims

2. Claims 58-66 and 68-70 are pending in the instant application. Claims 58-62 have been amended as requested by Applicant in the Paper filed July 10, 2006.

Maintained Rejections

Claim Rejections - 35 USC § 101 and § 112

35 U.S.C. 101 and 112, first paragraphs read as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.
>
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 58-66 and 68-70 remain rejected under 35 U.S.C. 101 and 112, first paragraph, because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, for reasons of record in the previous office actions, mailed May 19, 2004, and February 8, 2005, July 28, 2005, Feb. 10, 2006 and below.

Claims 58-66 and 68-70 also remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicants' arguments (pages 5-23, Paper filed July 10, 2006 and pages 2-4, Paper filed Sept. 6, 2006) have been fully considered but are not found to be persuasive for the following reasons.

Applicant relies on the gene amplification data for the gene encoding PRO274 polypeptide for patentable utility of the PRO274 polypeptide. The issue is whether or not amplified DNA correlates with increased mRNA, and whether or not increased mRNA levels correlates with increased protein levels. The art establishes that there is no strong correlation between gene amplification and increased mRNA or protein levels. See Pennica et al., and Gygi et al. of record.

Applicants submit that the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration, and accordingly, submit that in order to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that a person of ordinary skill in the pertinent art would doubt the truth of the statement of utility, and that the standard is not absolute certainty. Applicants submit that the law requires only that one skilled in the art should accept that such a correlation is more likely than not to exist. Applicants submit that the references cited by the PTO are either irrelevant, not contrary to Applicants' arguments, or actually offer support for Applicants' position. Applicants submit

that the teachings of Pennica et al. are specific to WISP genes, and say nothing about the correlation of gene amplification and protein expression in general, and that Gygi et al. supports Applicants position that there is a positive correlation between the overexpression of mRNA and protein.

While Gygi et al. provide data that demonstrate there is no correlation between abundance of protein and abundance of mRNA except for the most highly expressed proteins, and teach that there is a very slight positive correlation between mRNA and protein levels, Gygi et al. also state that mRNA abundance is a poor predictor of protein abundance (p. 7367, Col. 1, first full paragraph).

Applicants discuss the Chen et al. reference, and reiterate that no attempt was made to compare expression levels in normal versus tumor samples, and that the authors concede that they had too few normal samples for meaningful analysis (page 310, col. 2). Applicant asserts that as a result, the analysis in the Chen paper shows only that a number of randomly selected proteins have varying degrees of correlation between mRNA and protein expression levels within a set of different lung adenocarcinoma samples, and the Chen paper does not address the issue of whether increased mRNA levels in the tumour samples taken together as one group, as compared to the normal samples as a group, correlated with increased protein levels in tumour tissue versus normal tissue.

This has been considered but not found persuasive. The section in Chen referred to did not refer to the entire sample, but addressed determining whether the 21 genes showing a significant correlation between the protein and mRNA expression among all samples demonstrate changes in this relationship during tumour progression, and the correlations were

examined separately for stage I (n=57) and stage III (n=9) lung adenocarcinomas. The number of non-neoplastic lung samples (n=9) was insufficient for a separate correlation analysis of this group. Regarding the argument that Chen et al. did not examine the correlation between increases in mRNA and protein expression in tumor tissue as compared to normal tissue, and therefore Chen et al. is nor applicable to the application at issue, Chen et al. is support for the assertion that transcript levels do not necessarily correlate with protein levels.

Applicants on pages 8-9 of the response discusses Anderson et al., and submit that this reference looked at levels of mRNA in the same, non-disease state across different genes, and not changes in mRNA levels for a single gene, and Anderson et al. is not inconsistent with or contradictory to the utility of the instant claims and offers no support for the PRO's rejection of Applicants' asserted utility.

This has been considered but not found persuasive. Anderson et al. is support for the assertion that transcript levels do not necessarily correlate with protein levels.

Applicants on pages 9-10 of the response submit that the authors of Lian et al. themselves admit that there are a number of problems with the data presented in this reference, such as the insensitivity of Coomassie dye stain, and the low level of proteins examined (50) compared to the approximately 7000 genes for which mRNA levels were measured. Applicants submit on page 9 that only two genes meet the authors' criteria for differentially expressed mRNA level, and of those, one apparently shows a corresponding change in protein level an one does not.

These arguments have been considered but are not persuasive. When reading many if not most of papers in this field, the authors generally readily admit to limitations in the methods used. But these papers are published in peer reviewed journals and are therefore considered

relevant. Additionally, even if only two genes meet the authors' criteria for differentially expressed mRNA level and one shows a corresponding change in protein level and one does not, one of skill in the art would determine that it is not predictable that a change in mRNA would lead to a corresponding change in protein, and would determine empirically if this were the case.

Applicants on pages 11-13 discuss Fessler et al., who looked at proteins that were up or down-regulated and then looked at corresponding mRNA levels, and submit that in 5 of the 6 cases for which a change in mRNA levels are reported, the change in the level of mRNA corresponds to the change in the level of the protein. Applicants argue that changes in protein levels when mRNA levels are unchanged are not relevant, and that Fessler's results are consistent with Applicants' assertion that a change in mRNA level for a particular protein generally leads to a corresponding change in the level of the encoded protein.

Applicants' arguments have been fully considered but are not deemed persuasive. Fessler is evidence that there is a poor correlation between changes in levels of protein and corresponding changes in levels of mRNA, as the authors themselves state.

Applicants on page 13 submit that the Patent Office has failed to meet its initial burden of proof that Applicants claims of utility are not substantial or credible, and that the arguments presented by the Examiner in combination with the Pennica et al., Gygi et al., Chen et al., Anderson et al., and Fessler et al. papers do not provide sufficient reasons to doubt the statements by Applicants that PRO274 has utility. Applicants submit that the law does not require the existence of a "necessary" correlation between gene amplification and mRNA and protein expression levels, and assert that according to the authors themselves, the data in the above cited references confirm that there is a general trend between gene amplification and

mRNA and protein expression levels, which meets the "more likely than not standard" and show that a positive correlation exists between gene amplification and mRNA and protein expression. Applicants submit that the Examiner's reasoning is based on a misrepresentation of the scientific data presented in the above cited reference and application of an improper, heightened legal standard, and that contrary to what the Examiner contends, the art indicates that if a gene is amplified in cancer, it is more likely than not that the mRNA and encoded protein will also be expressed at an elevated level.

Applicants submit on pages that it is more likely than not for amplified genes to have increased mRNA and protein levels, and cite Ornoft et al., Hyman et al., and Pollack et al., (of record), as collectively teaching that in general, gene amplification increases mRNA expression. Applicants also cite the second Polakis Declaration, the assignee of the present application, which shows that in general, there is a correlation between mRNA levels and polypeptide levels.

Applicants' arguments with respect to Ornoft have been fully considered but are not found to be persuasive. Ornoft et al. appear to have looked at increased DNA content over large regions of chromosomes and compare that to mRNA and polypeptide levels from the chromosomal region. Their approach to investigating gene copy number was termed CGH. Ornoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. Ornoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (pg 40). This analysis was not done for PRO274 in the instant specification. Therefore, the relevance, if any of Ornoft et al. is not clear.

Applicants address the second Polakis Declaration, which will be addressed below.

Applicant has submitted teachings from Alberts, B. (Molecular Biology of the Cell (3rd ed 1994 and 4th ed 2002)) and Lewin, B. (Genes VI 1997) to support the statements of Dr. Polakis (Polakis II declaration; (below). Applicant also cites numerous references to emphasize that those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression (such as Zhigang et al., Meric et al. Orntoft et al., Wang et al., Munaut et al., etc., pages 17-23). Applicant asserts that changes in mRNA level generally lead to corresponding changes in the level of expressed protein. Applicant also contends that the references and the Polakis declaration establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein. Applicants submit a total of 118 references in addition to the declarations and references already of record which they assert supports Applicants' asserted utility, either directly or indirectly.

Applicant's references and arguments have been fully considered but are not found to be persuasive. While the Examiner acknowledges the teachings of Alberts and Lewin, which disclose that initiation of transcription is the most common point for a cell to regulate the gene expression, it is not the only means of regulating gene expression. For example, Alberts also teaches that there are a number of other controls that can act later in the pathway from RNA to protein to modulate the amount of protein that is made, including translational control mechanisms and mRNA degradation control mechanisms (see Alberts 3rd ed., bottom of pg 453). Meric et al. states the following:

> "The fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells. [M]ost efforts have concentrated on identifying differences in gene expression at the level or mRNA, which can be attributable to either DNA amplification or to differences in transcription."

However, Meric et al. also goes on to state that gene expression is quite complicated, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability (see page 971, Introduction). Meric et al. also teaches that there are a number of translation alterations encountered in cancer, including variations in the mRNA sequence as a result of mutations, alternate splicing and transcription start sites, alternate polyadenylation sites, and alterations in the components of the translation machinery (see pages 973-974). Also, with the exception of Futcher et al., all of Applicant's newly cited references are directed to the analysis of single genes, or a small group of genes, and therefore do not demonstrate trends found across proteins in general. The studies cited by Applicant that examine the expression of specific genes or small numbers of genes are not found persuasive in view of comprehensive studies where significantly larger numbers of transcripts and proteins were examined and more accurately describe general trends, specifically, Haynes (80 proteins examined) and Chen (165 proteins examined) (cited previously by Examiner) and Nagaraja et al. (2006), Waghray et al. (2001) and Sagynaliev et al. (2006) (described below).

While the vast majority of newly cited references are drawn to predictability of protein on the basis of mRNA amplification (and for reasons cited above do not merit further discussion), a single reference, that by Godbout, is pertinent to the issue at hand. However, the Examiner finds applicants interpretation of the reference to be erroneous. Far from teaching predictability for expression of PRO274 on the basis of a minor genomic amplification, the abstract of Godbout teaches "The DEAD box gene, DDX1, is a putative RNA helicase that is co-amplified with MYCN in a subset of retinoblastoma (RB) and neuroblastoma (NB) tumors and cell lines. Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a

number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified." The protein encoded by the DDX gene *had been characterized* as being a putative RNA helicase, a type of enzyme that *would be expected to confer a selective advantage* to the cells in which it (the DDX gene) was amplified. On page 21167, right column, first full paragraph, Godbout et al. state "*It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell* (48, 49). For example, although ERBA is closely linked to ERBB2 in breast cancer and both genes are commonly amplified in these tumors, ERBA is not overexpressed (48). Similarly, three genes mapping to 12q13-14 (CDK4, SAS and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region (GADD153, GL1, and A2MR) are rarely overexpressed in gene-amplified malignant gliomas (50, 51). The first three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons."

On the contrary, there is no structure/function analysis in the specification regarding the putative protein encoded by the PRO274 gene. It is not disclosed, and based upon the sequence searches in this case, the Examiner can not find any reason to suspect, that the protein encoded by the PRO274 gene would confer any selective advantage on a cell expressing it. It has no known homology to an RNA helicase or any other protein that would be expected to confer a selective advantage to a tumor cell. Further, it cannot be determined from the abstract whether the level of genomic amplification of the DDX1 gene was comparable to that disclosed for PRO274.

In summary, of applicants 118 references submitted, only a single one, Godbout, is drawn to the predictability of protein levels based upon genomic DNA amplification, and that one supports the Examiners assertion that it is more likely than not that the PRO274 protein would *not* be expected to be found in increased amounts in the cells tested by applicants, and thus has no utility as a cancer diagnostic.

An additional reference that provides evidence that gene amplification does not necessarily lead to increased transcript is Li et al., Oncogene, Vol. 25, pages 2628-2635, 2006. Li et al. used a functional approach that integrated simultaneous genomic and transcript microarray, proteomics, and tissue microarray analyses to directly identify putative oncogenes in lung adenocarcinoma. On page 2633, right column, Li et al. state: "*In our study, 68.8% of the genes showing over-representation in the genome did not show elevated transcript levels*, implying that at least some of these genes are 'passenger' genes that are concurrently amplified because of their location with respect to amplicons but *lack biological relevance in terms of the development of lung adenocarcinoma*."

In summary, it is clear that amplification of the genome more often than not does not result in increased mRNA expression.

With regard to Applicants' assertions that an increase in transcript levels correlates with an increase in proten levels, Applicants' references and arguments have been considered but not deemed persuasive. With the exception of Futcher et al., all of Applicant's newly cited references are directed to the analysis of single genes, or a small group of genes, and therefore do not demonstrate trends found across proteins in general. Nagaraja et al. (Oncogene, 25:2328-2338, 2006), provide data comparing transcript and protein levels between normal of cancer

tissue. Nagaraja et al. characterized comprehensive transcript and proteomic profiles of cell lines corresponding to normal breast (MCF10A), noninvasive breast cancer (MCF7) and invasive breast cancer (MDS-MB-231 and report that "the proteomic profiles indicated altered abundance of fewer proteins as compared to transcript profiles" (see abstract), and "the comparison of transcript profiles with proteomic profiles demonstrated that altered proteins were not always represented in the microarray designated profiles and *vice versa*" (see pg 2329, first column). Nagaraja et al. further report that, "a comparative analysis of transcripts and proteins to establish a relationship between transcript changes and protein levels has not yet become routine" (see pg 2328, second column). Lastly, Nagaraja et al. report that, "as dictated by post-transcriptional regulation, protein profiles showed far fewer changes as compared to transcript profiles" (see pg 2335, first column).

Similar results were reported by Waghray et al. (Proteomics, 1:1327-1338, 2001). Waghray et al. analyzed gene expression changes induced by dihydrostesterone (DHT) in the androgen responsive cancer line LNCaP, at both RNA and protein levels (see abstract). In this study, Waghray et al identified transcripts from 16750 genes and found 351 genes were significantly altered by DHT treatment and the RNA level, and identified 1031 proteins and found 44 protein spots that changed in intensity (either increased or decreased). Out of the 44 protein spots that changed in intensity, Waghray et al. reports that, "remarkably, for most of the proteins identified, there was no appreciable concordant change at the RNA level" (see pg 1333-1334, Table 4). Waghray et al. clearly state that, "The change in intensity for most of the affected proteins identified could not be predicted based on the level of the corresponding RNA" (see abstract).

In a review of gene expression in colorectal cancer (CRC), Sagynaliev et al. (Proteomics, 5:3066-3078, 2005) report that "it is also difficult to reproduce transcriptomics results with proteomics tools. Out of 982 genes found to be differentially expressed in human CRC by genome-wide transcriptomics technologies (Table 6a), only 177 (18%) have been confirmed using proteomics technologies" (see pg 3068).

In summary, it is clear that Nagaraja, Waghray and Sagynaliev support the Examiner's position that *changes* in mRNA expression frequently do not result in *changes* in protein expression. It is also noted that the specification of the instant application does not teach a change in mRNA level of PRO274.

In summary, it is clear that amplification of the genome more often than not does not result in increased mRNA expression and Nagaraja, Waghray and Sagynaliev support the Examiner's position that *changes* in mRNA expression frequently do not result in *changes* in protein expression. It is also noted that the specification of the instant application does not teach a change in mRNA level of PRO274. There are no teachings in the specification as to the differential expression of PRO274 mRNA in the progression of lung cancer or in response to different treatments of hormones (for example). Therefore, the Examiner maintains that Applicant's measurement of an increase of PRO274 genomic DNA does not support increased mRNA expression, or that even if mRNA levels were increased, the art teaches that there is a poor correlation between mRNA and protein levels. Therefore, the specification and cited references do not provide a specific and substantial utility for the encoded protein. Further research needs to be done to determine whether the purported increase in PRO274 DNA supports a role for the peptide in the cancerous tissue; such a role has not been suggested by the instant

disclosure. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. As discussed in Brenner v. Manson, (1966, 383 U.S. 519, 148 USPQ 689), the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and, "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Accordingly, the specification's assertions that the PRO274 polypeptides have utility in the fields of cancer diagnostics is not substantial.

Response to Applicants' Argument of Sept. 6, 2006:

Declarations by Dr. Polakis and Dr. Randy Scott:

The Declarations filed by Dr. Polakis and Dr. Randy Scott have been fully considered, but are not effective to overcome the rejection of claims 58-66 and 68-70 made under 35 U.S.C. 101/112, first paragraph.

Applicant refers to a second declaration of Dr. Polakis (Polakis II), submitted with the response (filed 10 July 2006). Applicant argues that this declaration provides the facts, set forth in a table (Exhibit B), for independent evaluation by the Examiner. The second Polakis declaration under 37 CFR § 1.132 filed 10 July 2006 is insufficient to overcome the rejection of claims 58-66 and 68-70 based upon 35 U.S.C. §101 and §112, first paragraph, for the following reasons. Specifically, data for PRO274 does not appear in the table (Exhibit B). Furthermore, it is not clear how the clones appearing in the table

compare to PRO274, or if the results presented in the table were determined by the same methodology as presented in Example 114 of the instant specification. In Example 114 or if the results presented in the table were determined by the same methodology as presented in Example 114 of the instant specification. For example, how highly expressed were the genes in Exhibit B that purportedly correlate with increased protein levels, 2-fold, 5-fold, 10-fold? How many samples were used? The declaration states that levels of mRNA and protein in tumor tissue were compared to corresponding normal tissue, but the amplification levels of genomic DNA from example 114 were compared to normal human blood, not corresponding normal tissue.

Applicant further submits a Declaration by Dr. Randy Scott in the response filed Sept. 6, 2006. Dr. Scott explains that DNA microarray technology is widely used and has an impressive commercial success. Dr. Scott states that although there are some exceptions on an individual gene basis, it has been a consensus in the scientific community that elevated mRNA levels are good predicator of increased abundance of the corresponding translated proteins in a particular tissue. Dr. Scott concludes that diagnostic markers and drug candidates can be readily and efficiently screened and identified using this technique, without the need to directly measure individual protein expression level. Applicant submits that Dr. Scott who has unparalleled experience with both the microarray technique and its industrial and clinical application, supports Applicant's position that this technique is not only mature, reliable and well accepted in the art, but also has been extensively used in drug development and in diagnosis of various diseases and produced enormous commercial success.

Dr. Scott's Declaration as well as Applicant's argument pertaining it have been fully considered, but are not deemed persuasive. The usefulness of the micrroarray technique and its commercial success are acknowledged. However, the issue at hand is whether a correlation between genomic DNA and mRNA is predictable, and futher whether a correlation between mRNA level and protein level is predictable. Therefore, although the instant specification discloses that the PRO274 genomic DNA is amplified in lung tumor, there is no disclosure as to the level of mRNA. Moreover, the commercial success of the micrroarray technique is immaterial to the instant invention, because evidence of commercial success, while sometimes persuasive as secondary evidence of non-obviousness, is irrelevant to utility and enablement. Finally, Applicant cites numerous references that allegedly show a correlation between mRNA and protein level and the Examiner cites numerous references that allegedly show that there are instances where there is no correlation between mRNA levels and the protein levels. Therefore, it is apparent that the state of the art is such that correlation between genomic DNA and mRNA levels, and mRNA and protein levels is unpredictable and should be determined on a case by case manner. Thus, data is needed showing there is a correlation between PRO274 genomic DNA, mRNA levels and the level of the PRO274 polypeptide, so that the level of reproducibility or the level of reliability of the results can be independently verified. Since the specification does not disclose any such data, it cannot be said that the microarray assay consistently and reliably results in high correlation between PRO274 mRNA levels and protein expression levels in lung tumor samples.

4. Claims 58-62 and 69-70 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis of this rejection is set forth in the Office Action mailed 19 May 2004, the Office Action mailed 08 February 2005, and the Office Action02 May 2005, the Office Action mailed 28 July 2005 and the Office Action mailed 10 February 2006. The specification discloses a single amino acid sequence for PRO274, SEQ ID NO: 7. There is a utility and enablement issue regarding whether or not the nucleic acid encoding PRO274 is amplified in lung tumors (see rejections under 35 U.S.C. §§ 101 and 112, first paragraph, above). Furthermore, the specification does not disclosure any variants of SEQ ID NO: 7, nor whether such sequences are amplified in lung tumors.

Applicant's arguments (pp. 24-27, remarks submitted July 10, 2006) have been fully considered but are not found to be persuasive for the following reasons.

Applicant urges that such provides basis for the claimed genus of native polypeptide sequences with at least 80-99% sequence identity to SEQ ID NO: 7 which are functionally defined as being encoded by a nucleic acid that is amplified in lung tumors. Applicant points to the specification's disclosure of methods for the determination of percent identity, and assays for identification of nucleic acids and for the functional limitation in the claims. Applicant urges that the skilled artisan can readily test native polypeptide sequences for identity and whether or not the encoding nucleic acids are amplified in lung tumors. This has been fully considered but is not found to be persuasive. The courts have specifically stated that if the skilled artisan cannot

envision the *detailed chemical structure* of an encompassed polypeptide, until the structure is disclosed, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Applicants submit that *Fiers v. Revel*, and *Amgen Inc. v. Chugai* do not apply to the claimed polypeptides, which dealt with written description of DNA. Applicants cite *Enzo Biochem., Inc. V. Genprobe, Inc.* in which the court adopted the standard that "the written description requirement can be met by 'showing that the invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics,.., i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Id. at 1324. Applicants submit that while the invention in Enzo was still a DNA, the holding has been treated as being applicable to proteins as well, and indeed, the court adopted the standard from the USPTO's Written Description Examination Guidelines, which apply to both proteins and nucleic acids. Applicants submit that current applicable case law holds that biological sequences are not adequately described solely by a description of their desired functional activities, and that the instant claims meet the standard set by the Enzo court in that the claimed sequences are defined not only by functional properties, but also by structural limitations, since it is well established that a combination of functional and structural features may suffice to describe a claimed genus.

Applicants submit that the present application is different from *Fiddes v. Baird.* in that a common structure features, such as sequence similarity, was not provided in the claimed genus, and in contrast, claims 58-62 clearly define both common structural features (sharing at least

80%-99% sequence identity) and functional limitations (being overexpressed in lung tumor cells).

Applicants' arguments have been fully considered but are not deemed persuasive, for reasons of record in the previous office actions. 80% identity to a described sequence is not a true structure. It is not disclosed which of the 80% amino acids are important for activity. Additionally, being overexpressed in tumors is not a functional property, but a characteristic.

It is believed that all pertinent arguments have been answered.

Conclusion

5. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nichol can be reached at (571) 272-0835.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

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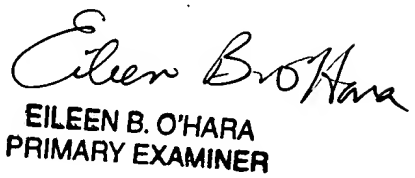

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